WO2004113285

Publication Title:

PROCESS FOR THE PREPARATION OF RACEMIC

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2004 (29.12.2004)

PCT

(10) International Publication Number
WO 2004/113285 A1

(51) International Patent Classification[7]: C07C 323/56, A61K 31/192

(21) International Application Number: PCT/GB2004/002599

(22) International Filing Date: 16 June 2004 (16.06.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0314260.1 19 June 2003 (19.06.2003) GB

(71) Applicant *(for AE, AG, AL, AM, AT, AU, AZ, BA, BB, BE, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CY, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, SZ, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW only)*: **ASTRAZENECA AB** [SE/SE]; Sodertalje, S-SE-151 85 (SE).

(71) Applicant *(for MG only)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London, Greater London W1K 1LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ANDERSSON, Kjell** [SE/SE]; AstraZeneca R & D Molndal, S-SE-431 83 Molndal (SE). **LINDSTEDT-ALSTERMARK, Eva-Lotte** [SE/SE]; AstraZeneca R & D Molndal, S-SE-431 83 Molndal (SE). **SORENSEN, Henrik** [SE/SE]; AstraZeneca R & D Molndal, S-SE-431 83 Molndal (SE).

(74) Agent: **ASTRAZENECA**; Global Intellectual Property, S-SE-151 85 Sodertalje (SE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR THE PREPARATION OF RACEMIC 2-{[2-(4-HYDROXYPHENYL)ETHYL]THIO}-3-[4-(2-{4-[(METHYLSULFONYL)OXY]PHENOXY}ETHYL)PHENYL]-PROPANOIC ACID

(57) Abstract: The present invention provides a process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent.

WO 2004/113285 A1

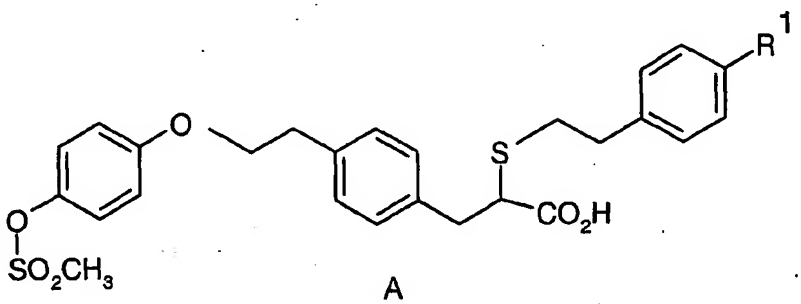
PROCESS FOR THE PREPARATION OF RACEMIC 2-{'2-(4-HYDROXYPHENYL) ETHYL!-THIO)-3-'4-(2-{4-'/METHYLSULFONYL)OXY ! PHENOXY}ETHYL)PHENYL! PROPANOIC ACID

Field of the invention

The present invention relates to a process for the preparation of certain of 3-phenyl-2-arylalkylthiopropionic acid derivatives which have utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome.

Background of the invention

Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula A



A

wherein R^1 represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof which are selective PPARα modulators. These compounds are useful in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome. The above compounds contain a chiral centre. Often one enantiomer is much more active than the other and the preferred enantiomer is obtained by a resolution process or by chiral chromatography. By its nature a resolution process of a racemic mixture leads to 50% of the undesired material being discarded. The situation can be improved if the undesired enantiomer can be converted back into a racemic mixture by a racemisation process. Therefore there is a need for an efficient and cost effective process for racemising the undesired isomer so that the resolution step can be repeated and reduce the material wastage in the process.

Description of the invention

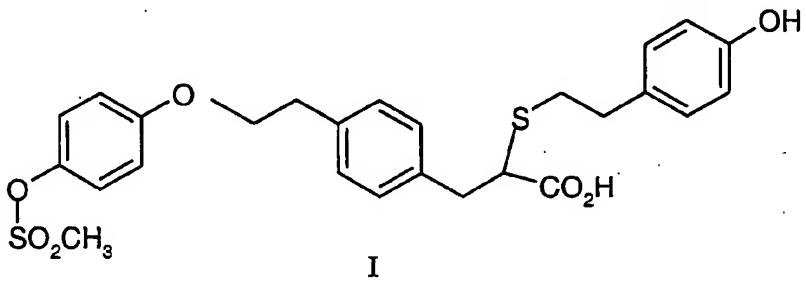
The present invention provides a process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]-propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one

enantiomer with a base in an inert solvent. Optionally the acid may be converted into an ester prior to racemisation or may converted into an ester during the racemisation. Suitable esters include C_{1-6} alkyl esters for example the methyl and ethyl ester. Suitable bases include potassium hydroxide or sodium hydroxide. Suitably the racemised ester is then hydrolysed to give the racemic acid for example by base hydrolysis or by acid hydrolysis.

In one aspect the process comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a halosilane in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C.

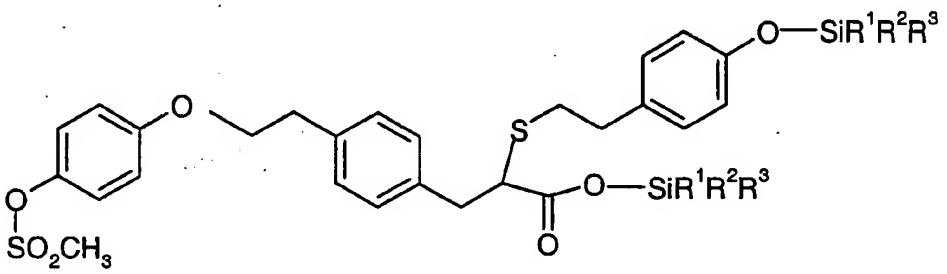
The term enriched means that one enantiomer comprises >50 %, preferably between 60 and 80% and most preferably between 80 and 100% of the 2-{[2-(4-hydroxyphenyl)-ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid in a mixture of the enantiomers of this acid.

In another aspect the present invention comprises reacting a compound of formula I



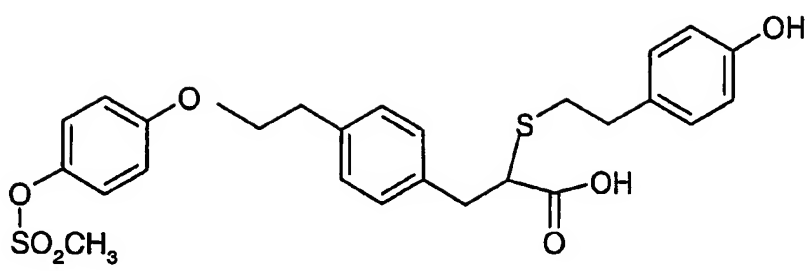
I

enriched in one enantiomer with a chlorosilane of formula $ClSiR^1R^2R^3$ in which R^1, R^2, and R^3 independently represent a C_{1-6} alkyl group or aryl in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula II



II

in which R^1, R^2, and R^3 are previously defined which is hydrolysed to give a racemic compound of formula III

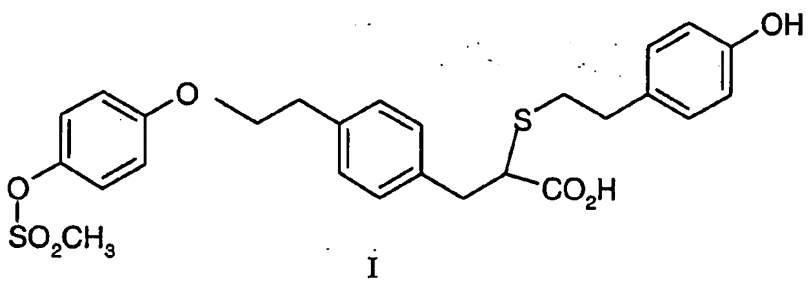


III

Suitable nitrogenous bases include 1,8 diazabicyclo[5.4.0] undec-7-ene, trialkylamines for example triethylamine, optionally substituted pyridines and optionally substituted imidazoles. Particularly the base is 1,8 diazabicyclo[5.4.0] undec-7-ene.

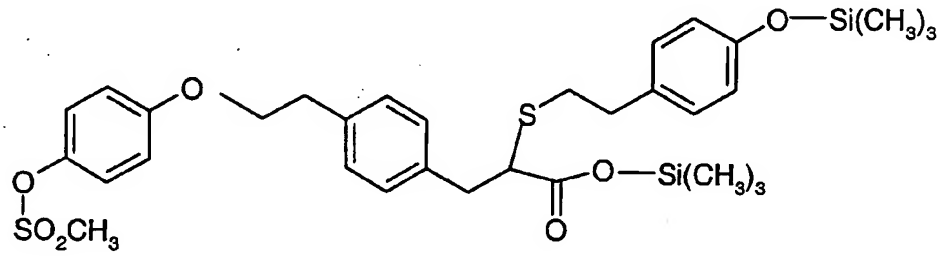
Suitable halosilanes include chlorotrialkyl silanes, for example chlorotriethylsilane and chlorodimethyl*tert*butylsilane and chlorotriarylsilanes for example chlorotriphenylsilane and mixed chloroarylalkyl silanes for example chlorodimethylphenyl silane. Particularly the chlorosilane is chlorotrimethylsilane.

In yet another aspect the present invention comprises reacting a compound of formula I



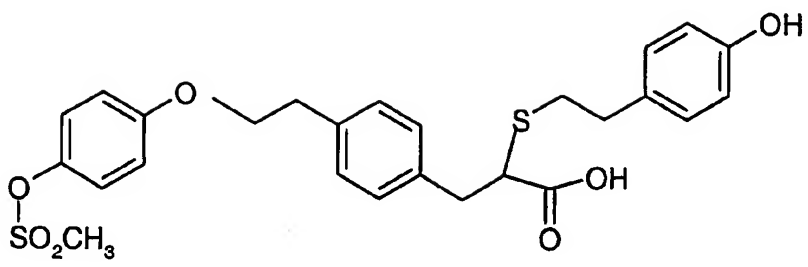
I

enriched in one enantiomer with chlorotrimethylsilane in the presence of 1,8 diazabicyclo[5.4.0] undec-7-ene in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula IV



IV

which is hydrolysed to give a racemic compound of formula III



III

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques. Hydrolysis is preferably carried out in the presence of an acid for example hydrochloric acid but basic hydrolysis may also be used.

The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield of the desired product. Suitable solvents include ethers, for example dialkyl ethers, especially diC_{1-6} alkyl ethers, or cyclic ethers for example tetrahydrofuran or hydrocarbons for example toluene.

Aryl means phenyl or naphthyl, preferably phenyl, each of which is optionally substituted by one or more C_{1-6} alkyl, C_{1-6} alkoxy or halo.

Preferably the enriched acid contains more of the (+)enantiomer (as measured in the conditions described below).

Examples

^{1}H NMR and ^{13}C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at ^{1}H frequencies of 300, 400, 500 and 600 MHz, respectively, and at ^{13}C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale (δ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Abbreviations

DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
DMF	*N,N*-dimethylformamide
THF	tetrahydrofuran
MeCN	acetonitrile
MeOH	methanol
TFA	trifluoroacetic acid

NH_4OAc	ammonium acetate
t	triplet
s	singlet
d	doublet
q	quartet
m	multiplet
bs	broad singlet

Preparation of Staring Material

2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid

(i) Methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate

2-(4-Aminophenyl)ethanol (11g, 81mmol) and 32ml conc HCl was dissolved in acetone and cooled to 0°C. Sodium nitrite (5.6g, 81mmol) in 20ml water was added dropwise. The temperature was kept under 0°C. After one hour, methyl acrylate (70g, 808mmol) and CuI (1.6g, 8mmol) were added (<0°C). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and water was added. The water phase was extracted three times with EtOAc, the organic phases were pooled and washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography using a 65:35 mixture of EtOAc and heptane as eluent. Further purification by preparative HPLC (using a gradient of CH_3CN/ 5%CH_3CN-waterphase containing 0.1M NH_4OAc as eluent) gave 9.7g product (yield 49%) as an oil.

^{1}HNMR (400MHz, $CDCl_3$): 2.84 (t, 3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

(ii) Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate

Triphenylphosphine (2.4g, 9mmol) was added to a solution of methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate (2.1g, 8.5mmol) and 4-(benzyloxy)phenol (1.7g, 8mmol) in 20ml toluene under nitrogen atmosphere. The solution was warmed to 55°C and diisopropyl azodicarboxylate (1.8g, 9mmol) was added. The reaction mixture was stirred at 55°C overnight. The mixture was allowed to cool and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography using a 80:20 mixture of heptane and EtOAc as eluent to yield 2.28g of the desired product (yield 61%) as colourless crystals.

^{1}HNMR (400MHz, $CDCl_3$): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29- 7.47 (m, 5H).

(iii) Methyl 2-chloro-3-{4-[2-(4-hydroxyphenoxy)ethyl]phenyl}propanoate

Methyl 3-(4-{2-[4-(benzyloxy)phenoxy]ethyl}phenyl)-2-chloropropanoate (1.0g, 2.4mmol) and dimethyl sulfide (0.9g, 14mmol) was dissolved in 60ml CH_2Cl_2. Boron trifluoride etherate (2.0g, 14mmol) was added dropwise to the stirred solution. The reaction mixture was stirred for two days at room temperature. Another equivalent (0.4g, 2.87mmol) boron trifluoride etherate was added and the stirring was continued overnight.

Water was added. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The organic phases were pooled, washed (water, brine), dried (Na_2SO_4) and evaporated under reduced pressure. Futher purification by preparative HPLC using a gradient of CH_3CN/ 5% CH_3CN-waterphase containing 0.1M NH_4OAc gave 0.55g of the desired product (yield 52%) as an oil.

^{1}HNMR (400MHz, $CDCl_3$): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

(iv) Methyl 2-chloro-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate

Methyl 2-chloro-3-{4-[2-(4-hydroxyphenoxy)ethyl]phenyl}propanoate (334mg, 1.0mmol) and triethylamine (303mg, 3.0mmol) was dissolved in 20ml dichlormethane and cooled to -20°C under nitrogen atmosphere. Methanesulfonyl chloride (114mg, 1.0mmol) was added dropwise. The mixture was allowed to reach room temperature. After 2 hours dichlormethane was added, the mixture was washed (water, brine), dried (Na_2SO_4) and evaporated under reduced pressure to yield 394mg pure product (yield 96%).

^{1}HNMR (400MHz, $CDCl_3$): 3.02-3.11 (m,5H), 3.15 (dd, 1H), 3.35 (dd,1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

(v) Methyl 2-({2-[4-(benzyloxy)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoate

2-[4-(Benzyloxy)phenyl]ethanethiol (334mg, 1.4mmol), methyl 2-chloro-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate (394mg, 0.95mmol) and potassium carbonate (189mg, 1.4mmol) were dissolved in 14ml dry DMF and stirred under nitrogen atmosphere at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in toluene. The organic phase was washed (water, brine), dried ($MgSO_4$) and evaporated. Futher purification by preparative HPLC using a

gradient of CH_3CN/5% CH_3CN-waterphase containing 0.1M NH_4OAc gave 477mg of the desired product (yield 75%).

^{1}HNMR (400MHz, $CDCl_3$): 2.76-2.89 (m, 4H), 2.95 (dd, 1H), 3.09 (m,5H), 3.20 (dd, 1H), 3.53 (m, 1H), 3.70 (s, 3H), 4.15 (t, 2H), 5.06 (s, 2H), 6.91 (m, 4H), 7.07-7.24 (m, 8H), 7.31-7.48 (m, 5H).

(vi) Methyl 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoate

To a solution of methyl 2-({2-[4-(benzyloxy)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate (477mg, 0.8mmol) and 15ml dichlormethane, dimethyl sulfide (239mg, 3.8mol) and boron trifluoride.etherate (545mg, 3.8mmol) were added. After 18 hours of stirring water was added to the reaction. The phases were separated and the aqueous phase was extracted twice with dichlormethane. The organic phases were pooled, dried ($MgSO_4$) and evaporated under reduced pressure.

274mg of the desired product (yield 67%) was obtained as an oil.

^{1}HNMR (400MHz, $CDCl_3$): 2.70-2.85 (m, 4H), 2.91 (dd, 1H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 4.13 (t, 2H), 6.72 (d, 2H), 6.87 (d, 2H), 6.99 (d, 2H), 7.10-7.22 (m, 6H)

(vii) 2-{[2-(4-Hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid

Methyl 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoate (105mg, 0.2mmol) was dissolved in 6.5ml of a 7:1 mixture of THF and water and cooled on an ice-bath. Lithium hydroxide (9.4mg, 0.4mmol) was added. Water was added to the reaction mixture after 24 hours of stirring at room temperature. The THF was evaporated under reduced pressure and the residue was acidified with 1M hydrochloric acid. The water phase was extracted with EtOAc (x3), the organic phases were pooled, washed (water, brine), dried ($MgSO_4$) and evaporated. The crude product was purified using preparative HPLC (eluent: CH_3CN / 5% CH_3CN-waterphase containing 0.1M NH_4OAc) to give 74mg of the desired product (yield 97%) as an oil.

^{1}HNMR (400MHz, $CDCl_3$): 2.68-2.95 (m, 5H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.47 (m, 1H), 4.12 (t, 2H), 6.70 (d, 2H), 6.86 (d, 2H), 6.97 (d , 2H), 7.12-7.21 (m, 6H).

^{13}CNMR (100MHz, $CDCl_3$): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

(viii) (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid

The racemate of 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)-oxy]phenoxy}ethyl)phenyl]propanoic acid was separated into its enantiomers using chiral chromatography. A Chiralpak AD JDB01+ AS003 (336 x 100 mm i.d.) and ethanol/formic acid 100/0.01% was used as mobile phase. The racemate (9 g) was dissolved in ethanol and injected onto the column. The first eluting peak was collected and UV-detected. The product (4.1 g) was obtained with an enantiomeric purity >99%. The optical rotation was found to be $[\alpha]^{20}_{D} = -33°$ by dissolving the enantiomer in methanol to give a concentration of 0.64 g/100ml. The optical rotation was measured at 20 °C using the sodium line at 589 nm. The (+) enantiomer is isolated subsequently from the column and is used as a starting material for the racemisation reaction.

^{1}H NMR (500 MHz, CD_3OD): 7.17-7.22 (6H, m), 6.99 (2H, d), 6.94 (2H, d), 6.69 (2H, d), 4.17 (2H, t), 3.46 (1H, t), 3.16 (3H, s), 3.13 (1H, dd), 3.05 (2H, t), 2.69-2.88 (5H, m).

Example 1

1,8 Diazabicyclo[5.4.0] undec-7-ene (DBU) (4.11g) was added by syringe over 5 minutes to a stirred mixture of (+)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid (3.83g) , toluene (8.65g) and tetrahydrofuran (44g) followed by the addition of chlorotrimethylsilane (2.24g) by syringe over 5 minutes. The resultant slurry was stirred at room temperature until the reaction was complete (3 hours). 2N Hydrochloric acid (31.2g) was added to the reaction mixture to hydrolyse the TMS ester, followed by brine. After separation of the aqueous layer, further brine was added, and the pH was adjusted to pH 2.5-3.5 by the addition of 1M sodium bicarbonate solution. The aqueous layer was separated and the organic layer was distilled at atmospheric pressure to remove water. Ethanol was added and a vacuum distillation carried out to remove THF and give a solution of racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]-propanoic acid in ethanol.

Claims:

1. A process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent.

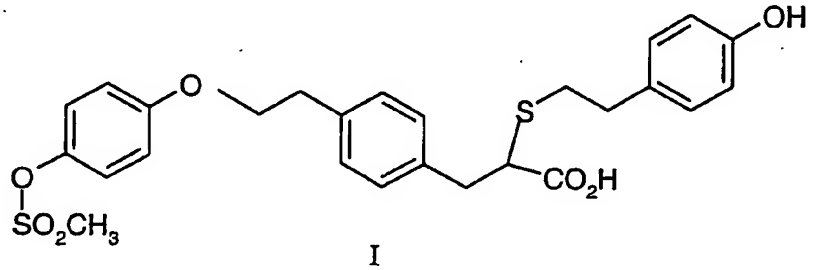
2. A process according to claim 1 wherein the acid is converted into an ester prior to racemisation or during the racemisation.

3. A process according to claim 2 wherein the racemised ester is then hydrolysed to give the racemic acid.

4. A process according to claim 1 comprising reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a halosilane in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C.

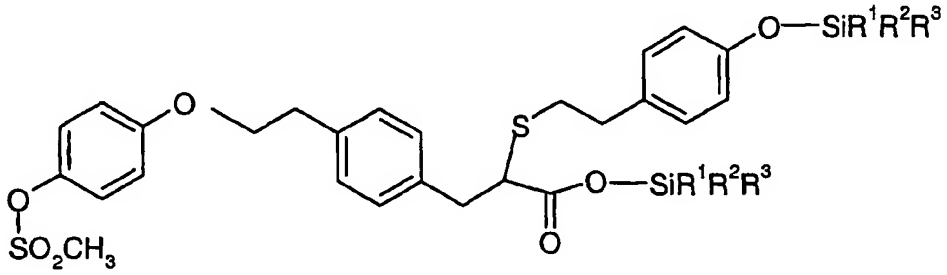
5. A process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)-ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]-phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with chlorotrimethylsilane in the presence of 1,8 diazabicyclo[5.4.0] undec-7-ene in the presence of an inert solvent at a temperature in the range of 0 to 150°C.

6. A process according to claim 4 comprising reacting a compound of formula I



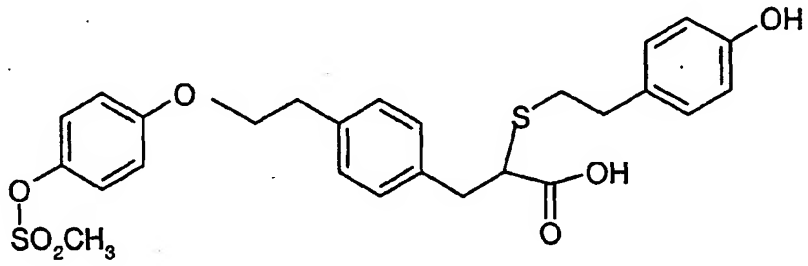
I

enriched in one enantiomer with a chlorosilane of formula $ClSiR^1R^2R^3$ in which R^1, R^2, and R^3 independently represent a C_{1-6} alkyl group or aryl in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula II



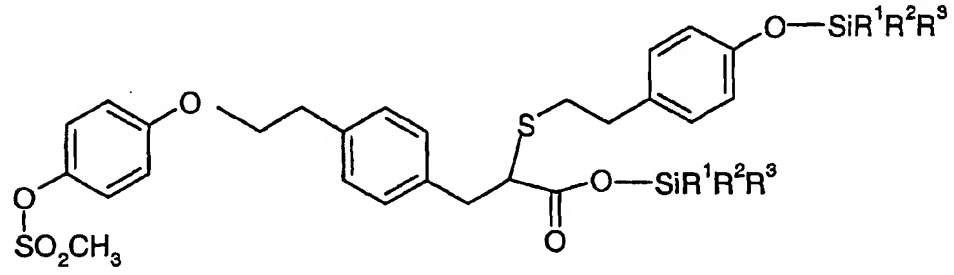
II

in which R^1, R^2, and R^3 are previously defined which is hydrolysed to give a racemic compound of formula III



III

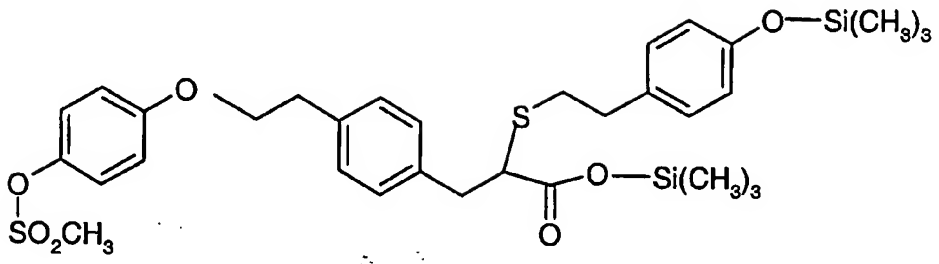
7. A compound of formula II



II

wherein R^1, R^2, and R^3 independently represent a C_{1-6} alkyl group or aryl.

8. A compound of formula IV



IV

INTERNATIONAL SEARCH REPORT

In nal Application No
PCT/GB2004/002599

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C323/56 A61K31/192

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/051826 A (ASTRAZENECA UK LTD ; BOIJE ANNA MARIA PERSDOTTER (SE); HOLM PATRIK (SE) 26 June 2003 (2003-06-26) cited in the application *the whole document; in particular, example 2 and the claims*	1-8
A	WO 99/62872 A (ANDERSSON KJELL ; ASTRA AB (SE)) 9 December 1999 (1999-12-09) *page 4, claims 1 and 5-11*	1-8
A	WO 99/62871 A (BOIJE MARIA ; INGHARDT TORD (SE); ANDERSSON KJELL (SE); ASTRA AB (SE);) 9 December 1999 (1999-12-09) *examples 1, 43 and 44*	1-8

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 August 2004	15/11/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lorenzo Varela, M.J.

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002599

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/21162 A (MERCK & CO INC) 10 August 1995 (1995-08-10) the whole document	1-8
X	DATABASE WPI Section Ch, Week 198641 Derwent Publications Ltd., London, GB; Class B05, AN 1986-233725 XP002293308 & JP 61 197530 A (MITSUBISHI GAS CHEM CO INC) 1 September 1986 (1986-09-01) abstract	1-8

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03051826 A	26-06-2003	WO 03051826 A1	26-06-2003
WO 9962872 A	09-12-1999	AT 246674 T	15-08-2003
		AT 251130 T	15-10-2003
		AU 752261 B2	12-09-2002
		AU 4667199 A	20-12-1999
		AU 752262 B2	12-09-2002
		AU 4667299 A	20-12-1999
		BR 9910921 A	06-03-2001
		BR 9910928 A	13-02-2001
		CA 2333938 A1	09-12-1999
		CA 2334374 A1	09-12-1999
		CN 1311772 T	05-09-2001
		CN 1312795 T	12-09-2001
		DE 69910203 D1	11-09-2003
		DE 69910203 T2	17-06-2004
		DE 69911770 D1	06-11-2003
		DE 69911770 T2	19-08-2004
		DK 1084103 T3	17-11-2003
		DK 1084102 T3	02-02-2004
		EE 200000720 A	15-04-2002
		EE 200000725 A	17-06-2002
		EP 1084103 A1	21-03-2001
		EP 1084102 A1	21-03-2001
		ES 2205844 T3	01-05-2004
		ES 2209457 T3	16-06-2004
		HK 1035711 A1	02-01-2004
		HR 20000782 A1	30-06-2001
		HU 0103226 A2	28-01-2002
		HU 0103376 A2	29-05-2002
		ID 28833 A	05-07-2001
		ID 29457 A	30-08-2001
		JP 2002516899 T	11-06-2002
		JP 2002516900 T	11-06-2002
		JP 2004043480 A	12-02-2004
		NO 20006115 A	07-02-2001
		NO 20006116 A	02-02-2001
		NZ 508452 A	30-05-2003
		NZ 508453 A	30-06-2003
		PL 344681 A1	19-11-2001
		PL 345205 A1	03-12-2001
		PT 1084103 T	31-12-2003
		PT 1084102 T	27-02-2004
		RU 2214999 C2	27-10-2003
		WO 9962872 A1	09-12-1999
		WO 9962871 A1	09-12-1999
		SI 1084103 T1	31-12-2003
		SI 1084102 T1	29-02-2004
		SK 17682000 A3	06-08-2001
WO 9962871 A	09-12-1999	AT 261429 T	15-03-2004
		AT 251130 T	15-10-2003
		AU 4667099 A	20-12-1999
		AU 752262 B2	12-09-2002
		AU 4667299 A	20-12-1999
		BR 9910913 A	06-03-2001
		BR 9910921 A	06-03-2001
		CA 2334107 A1	09-12-1999

INTERNATIONAL SEARCH REPORT

Inl nal Application No
PCT/GB2004/002599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9962871 A		CA 2334374 A1	09-12-1999
		CN 1312795 T	12-09-2001
		CN 1311769 T	05-09-2001
		DE 69911770 D1	06-11-2003
		DE 69911770 T2	19-08-2004
		DE 69915470 D1	15-04-2004
		DK 1084101 T3	14-06-2004
		DK 1084102 T3	02-02-2004
		EE 200000717 A	15-08-2001
		EE 200000725 A	17-06-2002
		EP 1084101 A1	21-03-2001
		EP 1084102 A1	21-03-2001
		ES 2209457 T3	16-06-2004
		HU 0103226 A2	28-01-2002
		ID 28164 A	10-05-2001
		ID 29457 A	30-08-2001
		JP 2002516898 T	11-06-2002
		JP 2002516899 T	11-06-2002
		NO 20006114 A	02-02-2001
		NO 20006116 A	02-02-2001
		NZ 508453 A	30-06-2003
		PL 344681 A1	19-11-2001
		PL 344682 A1	19-11-2001
		PT 1084102 T	27-02-2004
		WO 9962870 A1	09-12-1999
		WO 9962871 A1	09-12-1999
		SI 1084102 T1	29-02-2004
		SK 17672000 A3	06-08-2001
		SK 17692000 A3	10-05-2001
		TR 200003543 T2	20-04-2001
		TR 200003583 T2	21-05-2001
		TW 446694 B	21-07-2001
		TW 548263 B	21-08-2003
		US 6630600 B1	07-10-2003
		US 6362360 B1	26-03-2002
		ZA 200006771 A	20-05-2002
		ZA 200006773 A	20-02-2002
		AT 246674 T	15-08-2003
WO 9521162 A	10-08-1995	AT 206407 T	15-10-2001
		AU 691878 B2	28-05-1998
		AU 1696795 A	21-08-1995
		BR 9506727 A	23-09-1997
		CA 2180947 A1	10-08-1995
		CZ 9602272 A3	15-01-1997
		DE 69523038 D1	08-11-2001
		DE 69523038 T2	06-06-2002
		EP 0741712 A1	13-11-1996
		ES 2161863 T3	16-12-2001
		FI 963054 A	01-08-1996
		HU 76303 A2	28-07-1997
		JP 9508628 T	02-09-1997
		NZ 279734 A	27-05-1998
		RO 118292 B1	30-04-2003
		RU 2135482 C1	27-08-1999
		SK 100696 A3	05-03-1997
		TW 472047 B	11-01-2002
		WO 9521162 A1	10-08-1995

INTERNATIONAL SEARCH REPORT

	onal Application No
	PCT/GB2004/002599

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9521162 A		US 5663341 A	02-09-1997
JP 61197530 A	01-09-1986	DE 3683512 D1	05-03-1992
		EP 0193113 A1	03-09-1986
		US 4918196 A	17-04-1990